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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,954	06/25/2001	Hubert Jan Jozef Loozen	O/98414-US	9900

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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,954	LOOZEN ET AL.	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's amendment and response filed August 3, 2004 wherein claims 5-6 and 9-12 are cancelled; claim 2 has been amended.

Currently, claims 1-4 and 7-8 are pending in this application.

Claims 1-4 and 7-8 as amended now are examined on the merits herein.

Applicant's declaration of Antwan G. H. Ederveen (not inventor), submitted August 3, 2004 under 37 CFR 1.132, is acknowledged and will be further discussed below.

Applicant's amendment which amends claim 2 and cancels claim 10 filed August 3, 2004 with respect to the rejection of claims 2 and 10 made under 35 U.S.C. 112 second paragraph for insufficient antecedent basis of record stated in the Office Action dated April 9, 2003 have been fully considered and found persuasive to remove the rejection. Therefore, the said rejection is withdrawn.

The following is new rejection(s) necessitated by Applicant's amendment filed August 3, 2004.

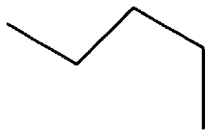
Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

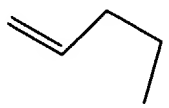
Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation "R_{11} is selected from the following group of side-chain structures" which is a butyl group in the claim as Compound (10) at page 14a:



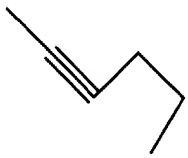
There is insufficient antecedent basis for this limitation in the claim R_{11} having a length of 4, since the independent claim 1 define "R_{11} having a length of from 5 to 9 carbons as the longest chain on carbon atom no. 11". Therefore, the dependent claim 2 is insufficient antecedent basis for this limitation in the claim.

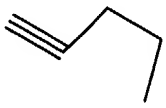
Note that the side chains in claims are drawn from compounds at page 14a:



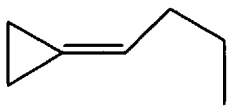
Compound (2)

Compound (5)





Compound (4)



Compound (8)

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Lobaccaro et al. (of record).

Lobaccaro et al. teach the active compounds, 11 -β-n-alkyl estradiol having ethyl, butyl, or decyl as R_{11}, which is the instant compound, and their compositions. See abstract, Scheme 1 compound 5b on page 2218, Table 1 on page 2219, Table 2 on page 2221, and the 4th paragraph of page 2224. Thus, the disclosure of Lobaccaro anticipates claim 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-4 and 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lobaccaro et al. (of record in the previous Office Action).

Lobaccaro et al. teach the active compounds, 11β-n-alkyl estradiol having ethyl, butyl, or decyl as R_{11}, which are homologs of the instant compounds, and their compositions. Lobaccaro also teaches that these compounds having R_{11} ethyl, butyl, or decyl, are known estrogenic compounds and also show antiestrogenic activity, and their compositions. See abstract, Scheme 1 compound 5b on page 2218, Table 1 on page 2219, Table 2 on page 2221, and the 4th paragraph of page 2224. Lobaccaro et al. further teaches that the substituent at the 11β-position increase and improve the binding affinity for the estrogen receptor (ER), and that the length of the11β-n-alky arm affects the binding affinity for the estrogen receptor and these compounds show EP-β antagonist and ER-α agonist activity (see page 2219 the right column to page 2221, Table 2).

Lobaccaro does not expressly disclose the particular 11β-n-alkyl estradiol herein having a length of from 5-9 carbon atoms, and the employment of these estradiol in a method for treating estrogen deficiency disorders and a method of inducing ER-α agonist activity and EP-β antagonist activity in a patient in need thereof.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular 11β-n-alkyl estradiol herein method for treating estrogen deficiency disorders and a method of inducing ER-α agonist activity and EP-β antagonist activity in a patient in need thereof.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the particular 11β-n-alkyl estradiol having

a length of from 5-9 carbon atoms in a method for treating estrogen deficiency disorders and a method of inducing ER-α agonist activity and EP-β antagonist activity in a patient in need thereof, since the estradiols of Lobaccaro having 2, 4, and 10 carbons at 11 -β-position are known estrogenic compounds and also show antiestrogenic activity, and thus one ordinary skill in the art would have expected the estradiol compounds of Lobaccaro to be useful in the method for treating estrogen deficiency disorders since estradiol compounds are well known to be useful the method for treating estrogen deficiency disorders.

Moreover, the substituent at the 11 -β-position in the compounds of Lobaccaro is known to increase and improve the binding affinity for the estrogen receptor according to Lobaccaro et al. Estrogen receptor affinity is known to discriminate two estrogen receptors, ER-α and EP-β. Further, the compounds of Lobaccaro et al. show ER agonist activity and ER antagonist activity. Therefore, one ordinary skill in the art would reasonably have expected the estradiol compounds of Lobaccaro to be useful a method of inducing ER-α agonist activity and EP-β antagonist activity in a patient.

The structure of the instant compounds having a length of from 5-9 carbon atoms in R_{11}, is substantially similar to the structures of their homologs having ethyl, butyl, or decyl as R_{11} in Lobaccaro. Moreover, the substituent at the 11β-position is known to increase and improve the binding affinity for the estrogen receptor, and the length of the 11 -β-n-alky arm affects the binding affinity for the estrogen receptor to have ER agonist activity and ER antagonist ER-α agonist

activity. Therefore, one of ordinary skill in the art would have reasonably expected that the compounds of Lobaccaro modified from having the length of 2, 4, and 10 carbons at 11 to the length of 5-9 carbons at 11 would have possess the same or similar activity as their homologs because of the substantially close structural relationship. It has been settled that the addition of CH_3 or several CH_2 groups to a known compound is not ordinarily patentable and prima facie obvious. See *In re Wood*, 199 USPQ 137. Further, Lobaccaro has clearly provided the motivation to the structure modification herein since he teaches that the substituent at the 11 -β-position increase and improve the binding affinity for the estrogen receptor, and the length of the11β-n-alky arm affects the binding affinity for the estrogen receptor, and also affects ER agonist activity and ER antagonist activity.

Thus, one of ordinary skill in the art would have reasonably expected that the instant compounds would be useful in the method for treating estrogen deficiency disorders and the method of inducing ER-α agonist activity and EP-β antagonist activity in a patient.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Claims 1, 3-4 and 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Napolitano et al. (of record in the previous Office Action).

Napolitano et al. teaches the active compounds, 11β-substituted estradiol derivatives having R_{11} with less than 5 carbon atoms, which are homologs of the

instant compounds, and their compositions. Napolitano et al. teaches that 11β-substituted estradiol derivatives therein are known estrogenic compounds as the estrogen receptors. See abstract and Table 1 on page 2776. Napolitano et al. also teaches that the compounds having 11β-substituted show high affinity for estrogen receptor (see particularly at "Introduction" page 2774).

Napolitano et al. does not expressly disclose the particular 11β-substituted estradiol herein having a length of from 5-9 carbon atoms, and the employment of these estradiol in a method for treating estrogen deficiency disorders and a method of inducing ER-α agonist activity and EP-β antagonist activity in a patient in need thereof.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular 11β-substituted estradiol herein in a method for treating estrogen deficiency disorders and a method of inducing ER-α agonist activity and EP-β antagonist activity in a patient in need thereof.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the particular 11β-substituted herein in a pharmaceutical composition and method for treating estrogen deficiency disorders since the estradiols of Napolitano are known estrogenic compounds and estradiol compounds are well known to be useful the method for treating estrogen deficiency disorders.

Moreover, the substituent at the 11 β-position in the compounds of Napolitano is known to have high binding affinity for the estrogen receptor according to Napolitano. Estrogen receptor affinity is known to discriminate two estrogen receptors, ER-α and EP-β. Therefore, one ordinary skill in the art would also have expected the estradiol compounds of Napolitano to be useful a method of inducing ER-α agonist activity and EP-β antagonist activity in a patient.

The structure of the instant compounds having a length of from 5-9 carbon atoms in R_{11}, is substantially similar to the structures of their homologs having about 5 carbons or less as R_{11} in Napolitano. Therefore, one of ordinary skill in the art would have reasonably expected that the instant compounds would have possess the similar activity as their homologs because of the substantially close structural relationship. It has been settled that the addition of CH_3 or several CH_2 groups to a known compound is not ordinarily patentable and prima facie obvious. See *In re Wood*, 199 USPQ 137. Thus, one of ordinary skill in the art would have reasonably expected that the instant compounds would be useful in the method for treating estrogen deficiency disorders and a method of inducing ER-α agonist activity and EP-β antagonist activity in a patient. Further, Napolitano is seen to provide the motivation to the structure modification herein since he teaches that the compounds having 11β-substituted show high affinity for estrogen receptor.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Response to Argument

Applicant's arguments and the declaration of Antwan G. H. Ederveen under 37 CFR 1.132 submitted August 3, 2004 with respect to the rejections of made under 35 U.S.C. 103(a) of record in the previous Office Action April 9, 2003 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

Applicant's arguments that unexpected results are present and the following data in the declaration of Antwan G. H. Ederveen have been fully considered but are not deemed convincing since Applicant's results shown in Table A of the declaration at page 4, primarily show that the mechanism of action - whether they would be estrogen receptor subtupes α or β, and different effects as ER-α agonist activity and EP-β antagonist. However, Applicant is reminded that the claimed methods herein are broadly for "treating estrogen deficiency disorder" and "inducing ERα agonist activity and ERβ antagonist activity" which clearly encompassing both ERα agonist activity and ERβ antagonist activity.

Therefore, whether the compounds herein are estrogen receptor subtupes α or β, and different effects as ER-α agonist activity and EP-β antagonist, are not deemed to be an essential and critical element of the claimed invention.

Thus, the results in Table A in the declaration are considered insufficient to establish any unexpected results in regard to the claimed methods herein.

In view of the foregoing, the evidence presented in specification herein is not seen to support the nonobviousness of the instant claimed invention over the prior art.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejections are adhered to.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is

(571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9307.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Primary Examiner, AU 1617
September 23, 2004